COMPARISON OF SQUAMOUS CELL CARCINOMA OF THE TONGUE IN YOUNGER AND OLDER GROUPS IN A GOVERNMENT TEACHING HOSPITAL IN TAMIL NADU, CHENNAI, INDIA.

Dissertation submitted to

THE TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY

towards the partial fulfillment for the degree of

MASTER OF DENTAL SURGERY

BRANCH – VI

ORAL PATHOLOGY & MICROBIOLOGY

MARCH 2010

DECLARATION BY THE CANDIDATE

I hereby declare that this dissertation entitled **"Comparison of Squamous cell carcinoma of the tongue in younger and older groups in a government teaching hospital in Tamil Nadu, Chennai, India."** is a bonafide work done under the supervision of **Dr. I. Ponniah, MDS.,** Associate Professor and Head, Department of Oral Pathology and Microbiology, Tamil Nadu Government Dental College and Hospital, Chennai - 600 003. I also declare that this work was done after careful and thorough analysis not amounting to any sort of plagiarisms or ethical deviations based on the retrospective records (1970 – 2009) of the Department of Oral Pathology and Microbiology.

Signature of the Candidate

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CERTIFICATE BY THE GUIDE

This is to certify that the dissertation entitled **"Comparison of Squamous cell carcinoma of the tongue in younger and older groups in a government teaching hospital in Tamil Nadu, Chennai, India."** is a bonafide work done by **Dr. Khadijah Mohideen** towards the partial fulfillment of the requirement for the degree of **MASTER OF DENTAL SURGERY** in the speciality of **ORAL PATHOLOGY AND MICROBIOLOGY (Branch VI),** under my supervision.

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ENDORSEMENT BY THE PRINCIPAL / HEAD OF THE INSTITUTION

This is to certify that the dissertation entitled **"Comparison of Squamous cell carcinoma of the tongue in younger and older groups in a government teaching hospital in Tamil Nadu, Chennai, India."** is a bonafide work done by **Dr. Khadijah Mohideen** under the supervision of **Dr. I. Ponniah, MDS.,** Associate Professor and Head, Department of Oral Pathology and Microbiology, Tamil Nadu Government Dental College and Hospital, Chennai – 600 003.

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DECLARATION

I **Dr. Khadijah Mohideen** do hereby declare that the dissertation titled **"Comparison of Squamous cell carcinoma of the tongue in younger and older groups in a government teaching hospital in Tamil Nadu, Chennai, India."** was done based on the archival samples and records (Department of Oral Pathology & Microbiology, Tamil Nadu Government Dental College & Hospital, Chennai - 600 003) in partial fulfillment of the requirements for the degree of **Master of Dental Surgery** in the speciality of **Oral Pathology & Microbiology (Branch VI)** during the course period **2007 - 2010** under the supervision of, **Dr. I. Ponniah,** MDS.

I declare that no part of the dissertation will be utilized for gaining financial assistance for research or other promotions without obtaining prior permission from the Tamil Nadu Government Dental College & Hospital.

I also declare that no part of this work will be published either in the print or electronic media except with those who have been actively involved in this dissertation work and I firmly affirm that the right to preserve or publish this work rests solely with the prior permission of the Principal, Tamil Nadu Government Dental College & Hospital, Chennai – 600 003, but with the vested right that I shall be cited as the author(s).

Signature of the PG Student

Signature of the HOD

Signature of the Head of the Institution

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ABSTRACT

Objectives:

To assess retrospective records of patients with tongue cancer (SCC) between October 1976 and December 2009 of patients over 35 years and less than 35 years of age in orders to determine the clinical, histological and molecular differences that would predispose towards early development of tongue cancer in younger patients.

Study Design:

The medical records of 219 consecutive patients diagnosed with squamous cell carcinoma (SCC) of the tongue between October 1976 and December 2009 was retrieved from the institutional oral pathology registry out of a total of 2225 SCC. They were divided into two groups; patients over 35 years of age and less than 35 years of age. Off the 219 tongue cancers, 26 were found in patients less than 35 years of age and the rest was found in older age group. The two groups were compared clinicopathologically and a subset of ten cases was selected on the basis of TNM status for immunohistochemistry with markers p27 and Cyclin D1 to observe variance at the molecular level.

Results:

SCC of the tongue comprised 9.84% of the total 2225 SCC. Off the 219 tongue SCC, 11.88% occurred in younger age group and 88.12% occurred in older age group. Clinically, the lateral border of the tongue was the most frequent site involved in both groups. Gender involvement showed equal distribution. Histopathologically, the distributions of different grades were equally found in both

groups. Immunohistochemically, no difference was found with regard to the expression of cyclin D1 and p27. Etiologically, irritating dental factors was a major risk factor in younger age group and traditional risk factors were major risk factors for the older age group. Both the groups showed a gradual increase in the number of cases recorded decade wise.

Conclusion:

This study found no significant differences between SCC (tongue) between younger and older age groups, except for predisposing cause. Further study is required to better understand the etiological difference.

Keywords:

Tongue carcinoma; young patients; India; Incidence; Chennai;

CONTENTS

LIST OF ABBREVATIONS

SCC	-	Squamous Cell Carcinoma
TNGDC&H	-	Tamil Nadu Government Dental College & Hospital
WD	-	Well Differentiated
MD	-	Moderately Differentiated
PD	-	Poorly Differentiated
NS	-	Not Specified
RE	-	Recurrent
T	-	Tumor Size
N	-	Nodal metastasis
M	-	Metastasis to distant organs
IHC	-	Immunohistochemistry
MMTR	-	Madras Metropolitan Tumor Registry
No.	-	Number
S. No.	-	Serial Number
OSCC	-	Oral Squamous Cell Carcinoma
CCND1	-	Cyclin D1
SCCOT	-	Squamous Cell Carcinoma Of Tongue
MTSCC	-	Mobile Tongue Squamous Cell Carcinoma
UTMDACC	-	University Of Texas M.D. Anderson Cancer Center
HPV / HSV	-	Human Pappilloma Virus / Herpes Simplex Virus

Introduction

Aims & Objectives

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BIBLIOGRAPHY

The reference format followed in this thesis conform to that set forth in "*Uniform requirements for manuscripts submitted to biomedical journals" (*Ann Intern Med 1997;126:36-47) and the style format is in accordance with Oral Surgery Oral Medicine Oral Pathology Oral Radiology and Endodontics.

TNM CLINICAL CLASSIFICATION

T	-	Primary tumor
TX	-	Primary tumor cannot be assessed
T0	-	No evidence of primary tumor
Tis	-	Carcinoma in situ
T1	-	Tumor 2 cm or less in greatest dimension
T2	-	Tumor more than 2 cm but not more than 4 cm in greatest dimension
T3	-	Tumor more than 4 cm in greatest dimension
T4 Lip	-	Tumor invades adjacent structures, e.g., through cortical bone, tongue, skin of neck
Oral cavity	-	Tumor invades adjacent structures, e.g., through cortical bon, into deep (extrinsic) muscle of tongue, maxillary sinus, skin
N	-	Regional lymph node
NX	-	Regional lymph nodes cannot be assessed
N0	-	No regional lymph node metastasis
N1	-	Metastasis in a single ipsi-lateral lymph node, 3 cm, or less n greatest dimension
N2	-	Metastasis in a single ipsi-lateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension, or in multiple ipsi-lateral lymph nodes, none more than 6 cm in greatest dimension , or in bilateral or contra-lateral lymph nodes, none more than 6 cm in greatest dimension
N2a	-	Metastasis in a single ipsi-lateral lymph node, more than 3 cm but

not more than 6 cm in greatest dimension

N2b - Metastasis in multiple ipsilateral lymphnodes, none more than 6 cm in greatest dimension

N2c - Metastasis in bilateral or contralateral lymphnodes, none more than 6 cm in greatest dimension

M - Distant metastasis

MX - Presence of distant metastasis cannot be assessed

M0 - No distant metastasis

M1 - Distant metastasis

HISTOPATHOLOGICAL GRADING

Well Differentiated carcinomas consists of sheets and nests of cells with obvious origin from squamous epithelium. These cells are generally large and show a distinct cell membrane, although intercellular bridges or tonofibrils often cannot be demonstrated. The nuclei of the neoplastic cells are large and may demonstrate a good deal of variability in the intensity of the staining reaction. Nuclei which stain heavily with hematoxylin are referred to as hyperchromatic. In the well differentiated lesion mitotic figures may be found, but they often do not appear to be especially numerous. Many of these mitotic figures are atypical, although this may be obvious only to an experienced histopathologist. One of the most prominent features of the well differentiated carcinoma is the presence of individual cell keratinization and the formation of numerous epithelial or keratin, pearls of varying size. In a typical lesion, groups of these malignant cells can be found actively invading the connective tissue in a vagarious pattern.

Moderately Differentiated carcinomas lose certain features, so that their resemblance to squamous epithelium is less pronounced. The characteristic shape of the cells and their arrangement may be altered. The growth rate of the individual cells is more rapid, and this reflected in the greater numbers of mitotic figures, the even greater variation in size, shape and tintorial reaction and the failures to carry out the function of a differentiated squamous cell, the formation of keratin.

Poorly Differentiated carcinomas bear little resemblance to their cell of origin and will often present diagnostic difficulties because of the primitive and

uncharacteristic histologic appearance of malignant, rapidly dividing cells. These cells show an even greater lack of cohesiveness and are extremely vagarious.

INTRODUCTION

Oral cancer is a serious public health problem associated with significant morbidity and mortality worldwide.

"Oral and pharyngeal cancer, grouped together, is the sixth most common cancer in the world. The review focuses primarily on several high-risk countries in an attempt to gain insight into the geographic variations in the incidence of this cancer in the globe and to relate the high incidence in some populations to their life style".[1]

It is believed that the disease usually affects men who have been exposed to long term use of cigarette smoking and alcohol consumption through the sixth to the eighth decades of life.

With an estimated half a million cases around the globe and the rising trends reported in some populations, particularly in the young, urgent public health measures are needed to reduce the incidence and mortality of oral and oropharyngeal cancer." The disease is on the increase in young adults and most UK cancer registries record 6% of all oral cancers in young people under the age of 45 years. Rates in Scotland are higher than in other parts of the UK for both men and women.[1]

India has always been cited as the country with the highest incidence in the world, though in some recent reports Sri Lanka and Pakistan are ranked at the top. In India alone over 100,000 cases are registered every year. According to Cancer Incidence in V Continents – vol. VIII14 one district of India (Bhopal) has the highest rate for cancers of both the tongue (10.9 per 100,000) and mouth (9.6 per 100,000) in the world.

Ahmadabad urban registry also showed a high rate of 9.3 per 100,000 for tongue cancer. The other urban cancer registries of India have rates between 3.4 and 6.0.[1]

According to the latest report by the Madras Metropolitan Tumor Registry (MMTR) the incidence of oral cancer is on decline, while the incidence of squamous cell carcinoma of the tongue is on the rise in recent years from the earlier estimated percentage of 3% to 6-7%, particularly among younger people despite the fact that most cases are not associated with the use of tobacco or alcohol.[2]

More ever, the time span for carcinogens such as tobacco and alcohol to exert a detrimental effect in these younger patients is relatively short.[22]

The underlying causes remain unknown at the moment for patients under 35 years of age and it seems to be a distinct biological entity. [2]

The physiologic response to risk factors by men and women and the clinical behavior of these cancers in the younger population may be different. The molecular mechanism, the pathogenesis of the disease, and the way in which it differs are still unclear.[51]

High importance is to be given to the examination of the potential risk factors and likely protective factors to control the occurrence of oral carcinoma in young patients of both genders.[11]

Very few studies related to the oral cancer in this population and the diversity of criteria used to describe age, anatomical sites, clinical stage, and aetiology have been reported making it difficult to arrive at a conclusion.[26]

The characteristic behavior of the squamous cell carcinoma in this age group can be better understood with the collection of additional standardized information.[21]

Oral carcinogenesis is a multistep process in which 6-10 genetic events lead to the disruption of the normal regulatory pathways that control basic cellular functions including cell division, differentiation, and cell death. In recent years, several alterations in the expression of tumor suppressor genes and oncogenes in the development of OSCC have been described.[45]

"*It has been found that cyclin D1 status is associated with tumor grade, lymph node metastasis and survival rate in head and neck SCCs. Most of the studies examined SCCs of tongue as a single tumor entity.*" [3]

In the present study the relationship between CCND1 and p27 expressions is to be established with the clinical parameters and histological differences to draw comparisons between young patient group and the older group that would predispose towards development of tongue cancer in younger patients.

AIM OF THE STUDY

To assess retrospective records of patients with tongue cancer (SCC) between October 1976 and December 2009 of patients over 35 years and less than 35 years of age.

OBJECTIVE OF THE STUDY

To determine differences between the two groups that could be attributed towards early development of cancers in patients less than 35 years of age.

REVIEW OF LITERATURE

CRITERIA FOR AGE SELECTION – YOUNGER GROUP

Hirota et al in 2006[4] conducted a study about the oral squamous cell carcinoma in young patients. The analysis of the study led to the conclusion that the average age in cases registered in literature as young bearers of SCC ranged from 30.8 to 34.2. It was also found that the largest part of the patients registered belonged to the male gender.

Shameena et al in 2008[5] studied the squamous cell carcinoma of tongue in young patients and arrived at the conclusion that characterization of young patients with head and neck SCC is arbitrary. Most authors consider young patients with SCC as those less than 40 years of age, even though others use as reference ages under 20 or 30 years. Age average in cases registered in literature as young bearers of SCC ranges from 30 to 34.2.

INCIDENCE

McGregor et al in 1983[6] conducted a retrospective study of squamous cell carcinoma of the tongue and lower oral cavity from which they concluded that the incidence in young people has remained relatively constant over the years of the study and that there is an increasing number of young people being seen, with a high of three patients in 1979; however, there were a total of approximately 70 new patients per year with these oral cancers.

Granizo et al in 1997[7] retrospectively reviewed reports titled “Squamous cell carcinoma of the oral cavity in patients younger than 40 years” and found a tendency

toward an increase in the incidence of squamous cell carcinoma in young patients. In years they observed an increase and one of their most striking initial findings was the high proportion of SCC in patients younger than 40 years (8.2% of all cases).

Myers et al in 2000[8] did a retrospective study titled "Squamous cell carcinoma of the tongue in young adults: Increasing incidence and factors that predict treatment outcomes" as the head and neck literature of that time had given increasing attention to squamous cell cancer of the oral tongue (SCCOT) in young adults, which was not categorized as a distinct clinical entity until 1975. Upon further comparison of the ratio of patients aged 40 years or younger with SCCOT to the total number of patients with SCCOT seen at University Of Texas M.D. Anderson Cancer Center (UTMDACC) for each year from 1963 to 1996, they found the percentage of cases of SCCOT occurring in young adults increased dramatically during this period from less than 10% of all cases to 15% to 25% of all cases in the mid-1990's. This increase was determined to not only at their institution but also in the US population at large.

Schantz et al in 2002[9] conducted a retrospective and collaborative study titled "Head and Neck Cancer Incidence Trends in Young Americans, 1973-1997, with a Special Analysis for Tongue Cancer" and concluded that tongue cancer in adults younger than 40 years increased approximately 60% during the same period. The results of many studies suggested that head and neck cancer, particularly oral tongue cancer, is increasing in young adults internationally. Results of the clinical analysis indicated that the percentage of young patients in the total tongue cancer population seen at the M.D. Anderson Cancer Center increased from 4% in 1971 to 18% in 1993.

The increase in the number of young patients with head and neck cancer seemed to be mainly caused by increased tongue cancer. Tongue cancer in young Americans ranked second to salivary gland cancer in all head and neck cancers and increased 62% comparing 1985-1997 and 1973-1984.

Iamaroon et al in 2004[10] studied 587 cases of oral squamous cell carcinoma in northern Thailand with a focus on young people and analyzed that oral SCC was not declining but appeared to be a constant problem in this northern Thai population, particularly in young people. These findings were similar to studies published in the USA. Many regions of the world including Australia, southern South America, Sweden, and India have shown an increased incidence of oral cancer. They demonstrated a high number of oral SCC in the young northern Thai persons (12.8%) compared with previous data (4-6%).

Llewellyn et al in 2004[11] studied the factors associated with delay in presentation among younger patients with oral cancer and noticed an alarming rise of approximately 6 fold in the incidence of oral cancer (particularly tongue) among younger adults (for patients aged 20 to 39 years, between 1960 and 1994) has been reported in Europe and in the USA.

Shiboski et al in 2005[12] did a study titled "Tongue and Tonsil Carcinoma – Increasing Trends in the U.S. Population Ages 20-44 years" in which from a population of 5024 oral tongue SCC reported between 1960 and 1994, 276 (5.5%) occurred among young adults (ages 20-39 years). The incidence of oral tongue SCC increased 5-fold among young men (0.06-0.32 per 100,000) and 6-fold among young women (0.03- 0.19 per 100,000) compared with only a 2-fold increase in older age groups. However, during

the same period, there was a statistically significant increase in the incidence of oral tongue SCC from 0.09 per 100,000 to 0.48 per 100,000 (APC= + 2.1; P<0.001), among younger whites ages 20-44 years, whereas the incidence of SCC in all other sites decreased. The annual incidence rates of oral tongue SCC between 1973 and 2001 were overall 2 times higher than rates of pharyngeal tongue SCC.

Mackenzie et al in 2006[13] did a study titled "Increasing incidence of oral cancer amongst young people: what is the aetiology?" and noticed that countries in Western Europe have experienced increases in incidence of approximately 3 fold within a generation, while some countries in eastern Europe, have recorded even larger, 8 fold increases and the increase in numbers of cases will, in the future, be proportionately greater.

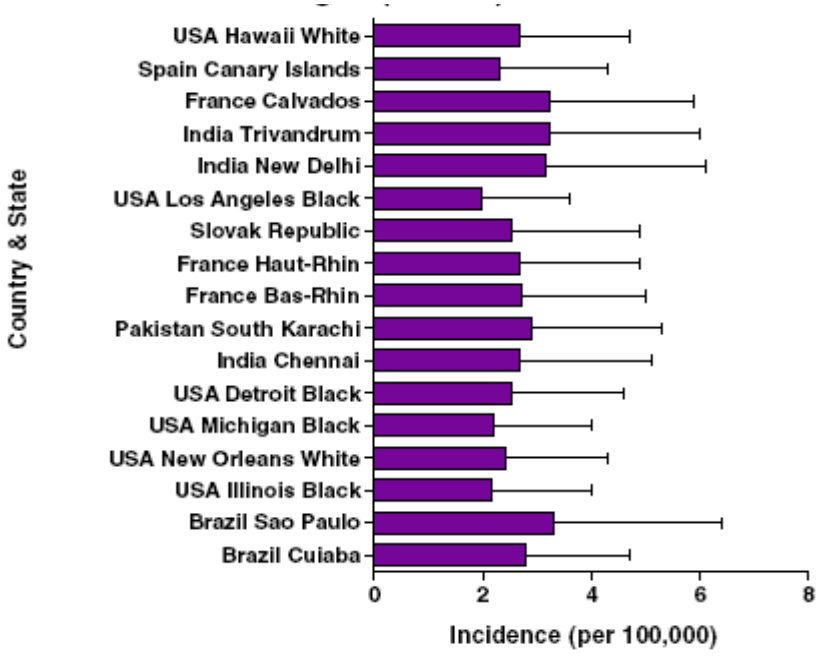
Warnakulsuriya et al in 2007[14] wrote a paper titled "Oral Cancer survival in young people in South East England" in which they describe that an alarming rise in the incidence of oral cancer among younger adults has been reported in Europe in the USA and in rest of the world. From US it was reported that between 1960 and mid 1980s male patients 30-39 years of age exhibited a nearly 4 fold increase in oral cancer incidence. This trend continued to 1990s for tongue cancer as the incidence increased 5 fold among young men and 6 fold increase in older age groups.

Garavello et al in 2007[15] under the research titled "Oral tongue cancer in young patients: A matched analysis" recognized an increase of 6-7% of carcinomas in young patients as compared to previous estimates of about 3%.

Papageorge et al in 2007[16] did a multi-centric, retrospective and collabrorative study titled "Etiology of oral cancer in the young patient: Is tongue cancer becoming the

other cancer in women?" in which they analyzed the combined tumor registry data from Denmark, Sweden, Norway, and Finland showed that between 1960 and 1994, 5.5% of the tongue cancers occurred in patients aged 20 to 39 years. This study also reported that the incidence of oral cancer in that 34-year time period increased 5 fold among young men and 6 fold among young women compared with only a 2 fold increase in the older age group.

Reference: Cancer registries worldwide, volume IX, IARC, 2007.



Age-standardised (world) incidence (per 100,000) and standard errors for tongue cancer in some high incidence countries and regions.

Hirota et al in 2008[17] wrote the paper titled "Risk factors for oral squamous cell carcinoma in young and older Brazilian patients: A comparative analysis" in which they confirm that there was a much higher incidence of this disease in the young patients (10.7%) than that reported by other authors, which has varied from 0.4 to 3.6%.

Warnakulasuriya et al in 2009[1] did a study titled "Global epidemiology of oral and oropharyngeal cancer" in which they have estimated that oral/pharyngeal cancers occurring in young people under the age of 45 is about 6%. In high-incidence countries of the world like Sri Lanka, India, Pakistan and Taiwan, parts of Western and Eastern Europe, parts of Latin America and the Caribbean and in Pacific regions many cases are reported before the age of 40. In Scotland, where this trend was first reported, the incidence rate between 1990 and 1999 in males under 45 has more than doubled from 0.6 to 1.3 per 100,000.

GENDER

Paymaster et al in 1957[18] did a study titled "The Problem of Carcinoma of the Tongue in India" by which they analyzed that carcinoma of the tongue was more frequent in men (80 per cent).

Dalitsch et al in 1959[19] published a paper titled "Oral cancer in women A study of the increasing incidence" in which they describe that carcinoma of the tongue was often found in the early years of life, and then occurred as frequently in females as in males.

Wawro et al in 1970[20] conducted a retrospective study titled "Cancer of the Tongue Experience at the Hartford Hospital from 1931 to 1963" through which they analyzed that a four to one predominance of male over female (80 per cent or 191 patients were male and 20 per cent or 47 patients were female) was present.

McGregor et al in 1983[6] did a study titled "Squamous Cell Carcinoma of the Tongue and Lower Oral Cavity in Patients under 40 Years of Age" by which they

analyzed that in patients under the age of 30 years, there was a female preponderance of 3:1. In patients over the age of 30 years, there was a slight male dominance.

Bursynski et al in 1992[21] did a study titled "Squamous cell carcinoma of the upper aerodigestive tract in patients 40 years of age and younger" in which women were afflicted more frequently than expected.

Llewellyn et al in 2003[22] did a multi-centric study titled "Squamous cell carcinoma of the oral cavity in patients aged 45 years and under: a descriptive analysis of 116 cases diagnosed in the South East of England from 1990 to 1997" in which they analyzed that a higher incidence of oral carcinoma in young women than young men, in contrast with the 2:1 male to female sex distribution observed in older patients.

Chitapanarux et al in 2006[23] conducted a study titled "Oral cavity cancers at a young age: Analysis of patient, tumor and treatment characteristics in Chiang Mai Hospital" in which they found the proportion of oral cavity cancer cases in women (40%) was higher than the average recorded in other literatures.

Siriwardena et al in 2006[24] published a paper titled "Demographic, aetiological and survival differences of oral squamous cell carcinoma in the young and the old in Sri Lanka" in which they reported that the male gender showed a predominance with the ratio of 4:1 and 3.6:1 in younger and older group respectively.

Regan et al in 2006[25] did a study titled "Squamous cell carcinoma of the head and neck in young Irish adults" in which it was noted that a number of studies of young patients with SCC of the head and neck it has been noted that there is a distinct group of younger patients, particularly women.

Garavello et al in 2007[15] did a comparative study titled "Oral tongue cancer in young patients: A matched analysis" in which they analyzed that the proportion of women was greater than in general population of tongue malignancies.

Ribeiro et al in 2009[26] did a comparative study titled "Clinical and histopathological analysis of oral squamous cell carcinoma in young people: A descriptive study in Brazilians" in which they concluded that 38 (83%) of the cases were found in men and only 8 (17%) in women, a ratio of 1:4.75. These findings were in accordance to the studies of Llewellyn et al. and Iamaroon et al. that reported higher incidences in men under 45 years old.

SITE

McGregor et al in 1983[6] under the study titled "Squamous cell carcinoma of the tongue and lower oral cavity in patients less than 40 years of age" predict that the tongue was by far the most common site. Carcinoma of the tongue was the dominant lesion in this group of young patients and occurred in 27 of the total group of 36 patients.

Kuriakose et al in 1992[27] did a comparative study titled "Comparison of Oral Squamous Cell Carcinoma in Younger and Older Patients in India" in which they analyzed that carcinomas in the >60 years age group occurred with similar frequency in the tongue and buccal mucosa but, in <35 years age group, tumors were more common in the tongue and these changes were statistically significant ($P < 0.04$).

Amador et al in 1995[28] did a study in cancer of the mobile tongue in Mexico. In their study MTSCC frequently involved the lateral borders, thus reflecting the susceptibility of this area to the development of carcinoma.

Granizo et al in 1997[7] published a paper titled "Squamous cell carcinoma of the oral cavity in patients younger than 40 years" in which they go on to say that all patients with SCC of the oropharynx had a previous history of tobacco and alcohol use, whereas tumors arising in patients without these carcinogenic factors were more often located on the tongue and the floor of the mouth. This observation agrees with previous research that showed an increase in the site of the tumor depending on the etiologic factor analyzed.

Iype et al in 2001[29] did a study titled "Oral cancer among patients under the age of 35 years" in which they analyzed that out of 264 patients observed, tongue was the commonest site identified in 136 patients followed by buccal mucosa in 69 patients.

Shiboski et al in 2005[12] published a report titled "Tongue and Tonsil Carcinoma – Increasing Trends in the U.S. Population Ages 20-44 years" in which they say that the proportion of oral tongue SCC was higher than any other sites in the younger age group (39%), but not in the older age group (23%).

Sasaki et al in 2005[30] did a study titled "Clinico-pathological features of squamous cell carcinoma of the oral cavity in patients < 40 years of age" in which their analysis by site showed that 54.3% of cancers arose on the tongue in young patients, compared with 30.9% in older patients, supporting previous studies suggesting that tongue may be more commonly affected in younger patients.

Chitapanarux et al in 2006[23] did a retrospective study titled "Oral cavity cancers at a young age: Analysis of patient, tumor and treatment characteristics in Chiang Mai Hospital" by which they reviewed the medical records of oral cavity cancer patients occurring before the age of 45 who were treated at Chiang Mai university Hospital from

1999-2003. A total of 20 patients were studied. The most common site was oral tongue (75%).

Elango et al in 2006[31] did a study titled "Trends of head and neck cancers in urban and rural India" in which they observed an increase of incidence of tongue cancers.

Siriwardena et al in 2006[24] did a comparative study titled "Demographic, aetiological and survival differences of oral squamous cell carcinoma in the young and the old in Sri Lanka" in which they confirm that tongue was the commonest site for younger group (41%, $P<0.01$) whilst buccal mucosa (37.5%, $P<0.05$) and alveolar mucosa (25%, $P<0.01$) were for older group.

Regan et al in 2006[25] under the study titled "Squamous cell carcinoma of the head and neck in young Irish adults" say that carcinomas of the anterior two-thirds of the tongue were significantly more common in younger patients.

Papageorge et al in 2007[16] conducted a study titled "Etiology of oral cancer in the young patient: Is tongue cancer becoming the other cancer in women?" from which it is evident that tongue cancer is the most common cancer in the oral cavity and has been widely regarded as a disease that predominantly affects men. Approximately 45% of tongue cancers occur in the posterior lateral border of the tongue, and 25% occur in the posterior one third or base of the tongue.

RISK FACTORS

Dalitsch et al in 1959[19] did a study titled "Oral cancer in women: A study of the increasing incidence" in which they mention oral sepsis and dental neglect as often being

a marked feature in their patients. Of sixty-five patients, 63 per cent had “bad,” “poor” or “irritating” dental conditions.

Sharp et al in 1964[32] did a study in carcinoma of the tongue. In their study they said that some degree of inflammation was present in all of the patients, from those with periodontal disease to those with gross oral sepsis of primary origin or secondarily due to trauma of dental or mechanical stimuli. These inflammatory changes usually are observed in patients who have thin, atrophic mucous membranes and cannot tolerate normal traumas of the mouth. These same abnormal states of the oral epithelium were found in all of their patients with lingual carcinoma.

Wawro et al in 1970[20] conducted a study titled “Cancer of the Tongue Experience at the Hartford Hospital from 1931 to 1963”. In their study they concluded common history of carious teeth, excessive smoking of all tobacco products, and the abuse of alcohol are the causative factors.

Byers et al in 1975[33] conducted a research titled “Squamous Cell Carcinoma of the Oral Tongue in Patients Less Than Thirty Years of Age”. In their study they said usual concomitant factors, such as heavy smoking, drinking, and poor dental hygiene, were absent for younger patients.

Amichetti et al in 1989[34] In his review titled “Squamous Cell Carcinoma of the Oral Tongue in Patients Less than Fifteen Years of Age”; several factors were mentioned as possible aetiological factors: irritative factors such as orthodontic appliances, dental caries and gold crowns, dietary factors and viral factors. In their case they suggest a possible role of sucking and chewing plastic materials as a possible exposure to

carcinogens (PVC), or chronic irritation, or both. They concluded that it is possible that in young patients a multi-factorial aetiology for this neoplasm must be considered.

Kuriakose et al in 1992[27] conducted a research titled "Comparison of Oral Squamous Cell Carcinoma in Younger and Older Patients in India" they observed that no obvious aetiological factors characterized younger patients with oral cancer, especially those with cancer of the tongue. For example, some 88% (22/25) of patients aged <35 years with lingual carcinoma had no evidence of aetiological factors, whilst only 8.3% (1/12) of patients over 60 years with tongue tumors were characterized by the absence of causative agents.

Marshall et al in 1992[35] did a study relating to Smoking, Alcohol, Dentition and Diet in the Epidemiology of Oral Cancer. In which it has been clearly documented that smoking and alcohol use increase the risk of oral cancer, and it is suspected, that poor oral hygiene or compromised dentition might also increase risk.

Bursynski et al in 1992[21] published a paper titled "Squamous cell carcinoma of the upper aerodigestive tract in patients 40 years of age and younger" in which they noted that generally implicated etiologic factors may not apply fully to this age group.

Ma R et al in 1995[36] conducted a preliminary investigation of an association between dental restorations and carcinoma of the tongue. They suggested that dental restoration may be a component in the process of carcinogenesis of SCC of the tongue in a small subset of patients. Regardless of the causative mechanism, dental restorations may act as a possible cofactor in conjunction with other known risk factors such as alcohol and tobacco.

Granizo et al in 1997[7] did a study titled "Squamous cell carcinoma of the oral cavity in patients younger than 40 years" in which they assessed a lack of association with common carcinogenic-related habits such as tobacco and alcohol use in 40% of men and 55.5% of women of the young patients.

Vellya et al in 1998[37] did a study on "Relationship between dental factors and tract cancer risk of upper aerodigestive". They concluded oral health characteristics, such as poor dentition, trauma due to ill-fitted dentures, either partially or totally, sharp or broken teeth, and low frequency of oral hygiene have also been suspected to be associated with oral cancers. The nature of the association with dental variables is difficult to pinpoint, however, because of the potential confounding effect of lifestyle determinants, such as tobacco, alcohol, and diet, as well as of socioeconomic and cultural characteristics.

Lockhart et al in 1998[38] did a retrospective study titled "Dental factors in the genesis of squamous cell carcinoma of the oral cavity" in which they analyzed that long-standing irritation from chronic periodontal disease, poor oral hygiene, ill-fitting dentures, sharp teeth, mouthwashes, electrogalvanism and edentulism have all been implicated as cofactors in the genesis of oral cancer. Of 86 indigent patients with tongue cancer, but with no control group, 44% had a site of persistent mechanical irritation by sharp teeth or dentures, usually in the denture flange area of full lower dentures. Clearly there are people with many years of chronic mucosal irritation from a dental or prosthetic source who do not develop cancer, but their study suggests that of those that do, a high percentage of these cancers will arise in areas of direct contact with teeth and appliances. They also found that the oral cavity is exposed to a wide variety of chemicals, trauma,

organisms, thermal changes, variations in moisture, foods, smoke and airborne substances, radiation, and foreign materials, some of which are known carcinogens and possible co-carcinogens. Host factors, such as age, genetic inheritance and humoral and cellular immunity, play obvious but poorly understood roles.

Hart et al in 1999[39] through their research titled "Oral and oropharyngeal squamous cell carcinoma in young adults: A report on 13 cases and review of the literature" noted that the most frequently implicated etiologic agents such as tobacco and alcohol use were not prevalent and thus not contributory in their patient populations' carcinogenesis. It is unclear why these individuals developed their cancers at a young age. Undoubtedly, these malignancies are the result of the interactions of constitutional and environmental factors.

Myers et al in 2000[8] did a study titled "Squamous cell carcinoma of the tongue in young adults: Increasing incidence and factors that predict treatment outcomes" analyzed that of 25 patients younger than 35 years with SCCOT treated in India showed that the rate of tobacco use or betel quid chewing was low in these patients relative to the rate seen in older patients.

Iype et al in 2001[29] did a multi-centric study titled "Oral cancer among patients under the age of 35 years" in which they observed that even though tobacco and alcohol abuse are said to be the main etiological factors a significant proportion of their young patients did not have associated risk factors for cancer. The number of habitués was higher in buccal mucosa cancer (79.7%) compared to tongue cancer (49%). This may point to the fact that tobacco habits are a major determinant of buccal mucosa cancer

compared to tongue cancer; the latter seemed to have a different aetiology at younger age.

Llewellyn et al in 2001[40] conducted a study titled "Risk factors for squamous cell carcinoma of the oral cavity in young people - a comprehensive literature review" in which they suggested that patients without typical risk factors for developing SCC of the oral cavity may have a worse prognosis compared with patients with the usual risk factors such as history of excessive tobacco and alcohol use. It is also concluded that the risk factors for oral cancer in the young were multi-factorial as some individuals displayed behavioral habits similar to those of older patients whereas others reported no such habits. Exposure to other forms of a carcinogen or other agents not traditionally recorded in hospital noted could have been contributing factors in the aetiology of oral cancer. They found that the proportion of patients with oral cancers (excluding buccal mucosa) and without habits (chewing/smoking tobacco and /or alcohol consumption) under the age was significant ($P<0.001$).

Schantz et al in 2002[9] conducted a retrospective and collaborative study titled "Head and Neck Cancer Incidence Trends in Young Americans, 1973-1997, with a Special Analysis for Tongue Cancer" and concluded that tongue cancer in adults younger than 40 years increased approximately 60% during the same period. The results of many studies suggested that head and neck cancer, particularly oral tongue cancer, is increasing in young adults internationally. Results of the clinical analysis indicated that the percentage of young patients in the total tongue cancer population seen at the M.D. Anderson Cancer Center increased from 4% in 1971 to 18% in 1993. Suspected etiologic agents include smokeless tobacco, various forms of drug abuse, virus, and host

susceptibility factors. However, no clear evidence exists to support the significance of any single determinant, including the role of tobacco. The increase in the number of young patients with head and neck cancer seemed to be mainly caused by increased tongue cancer. Tongue cancer in young Americans ranked second to salivary gland cancer in all head and neck cancers and increased 62% comparing 1985-1997 and 1973-1984.

Llewellyn et al in 2004[11] further conducted a study titled "Factors associated with delay in presentation among younger patients with oral cancer" in which they observed that the relatively short duration of exposure and the substantial number of cases without any known risk factors, particularly amongst females, however, suggested that factors other than tobacco and alcohol may also be implicated in the development of oral cancer in a proportion of these younger patients. Recent evidence, further, suggested an absence of traditional risk factors in a significant proportion of younger patients, especially amongst females. Thus, it has been suggested that oral cancer in the young may be a disease distinct from that occurring in older patients with a different aetiology and disease progression. However, the relative rarity of oral cancer occurring in relatively younger adults and the diversity in reporting age criteria, sites, stages and undisclosed aetiology, make comparisons between studies problematic.

Guneri et al in 2005[41] did a multi-centric study titled "Primary oral cancer in a Turkish population sample: Association with socio-demographic features, smoking, alcohol, diet and dentition" by which they determination that the association of poor dentition, poor oral hygiene and denture sores with oral cancer has been reported previously. In Turkey, poorer oral hygiene and fewer teeth were reported in cancer

patients and that people who are in high risk group for oral cancer have less frequent routine dental examinations.

Shiboski et al in 2005[12] did a study titled "Tongue and Tonsil Carcinoma – Increasing Trends in the U.S. Population Ages 20-44 years" in which they noted that even though oral SCC is strongly associated with a lifetime history of cigarette smoking and alcohol consumption in older adults (age > 55 years), to their knowledge little was known about potential risk factors associated with this disease in younger patients. It revealed that only few studies had reported a high proportion of heavy smoking and alcohol consumption among younger patients with oral carcinoma whereas the majority of studies found no such association.

Hirota et al in 2006[4] conducted a research titled "Oral squamous cell carcinoma in a young patient-Case report and literature review" by which they noted that a widely debated aspect of SCC in young patients regards etiological factors associated to the development of the disease. This interest was based on the fact that risk factors (smoking and drinking) that are usually observed in elderly patients are not verified in young ones. Despite the demonstration by some studies that the same etiological factors are present for both age ranges, the possibility of the existence of a carcinogenic action of tobacco and alcohol in the young patient is low, given that in this group exposure time would be relatively short for the establishment of a cause-effect relation. Thus, other factors should be investigated in order to explain SCC etiology in young patients, among which are included: genetic predisposition, previous viral infection, feeding habits, states immunodeficiency, and occupational exposure to the carcinogenic factor, socioeconomic condition and oral hygiene.

Elango et al in 2006[31] published a paper titled "Trends of head and neck cancers in urban and rural India" in which they stated that the increase in incidence of tongue cancer suggests factors other than tobacco and alcohol in its genesis.

Chitapanarux et al in 2006[23] published a paper titled "Oral cavity cancers at a young age: Analysis of patient, tumor and treatment characteristics in Chiang Mai Hospital" by which they analyzed an increase in the incidence of oral cavity cancers in female who never consumed alcohol or tobacco in the recent years and that oral cavity cancer in the young had a different etiology and natural history.

Siriwardena et al in 2006[24] did a multi-centric study titled "Demographic, aetiological and survival differences of oral squamous cell carcinoma in the young and the old in Sri Lanka" in which they concluded that 39% of cancers in younger group were not associated with any identifiable risk factor ($P<0.01$) and 70% of SCC of the tongue has no associated habits ($P<0.01$). Although all the patients with squamous cell carcinoma of the tongue in the older group practiced some kind of a habit (betel/alcohol/smoking), the same was 30% in the younger group. The difference with regards to habit and tongue cancers in younger group is statistically significant ($P<0.01$). The less intense association of tobacco chewing for the occurrence of oral squamous cell carcinoma in younger individuals raises the possibility of having other unidentified aetiological/risk factors for oral squamous cell carcinoma.

Regan et al in 2006[25] did a study titled "Squamous cell carcinoma of the head and neck in young Irish adults" in which they analyzed that other possible aetiological agents include drug abuse, viral infections, sexual practices, and diet, but there is no evidence of a strong association between any of these factors and the development of

SCC of the head and neck in young patients. Chronic iron deficiency anemia leads to mucosal atrophy and it has been suggested that this may lead to an increased susceptibility to carcinogens. Most of the 17% in their study who had never smoked were under 40 years of age, and all those under 30 years old had never smoked. Their finding was similar to those of other groups who have looked at people under 30 and found an absence of risk factors in 52% and 61% of them, respectively.

Papageorge et al in 2007[16] did a study titled "Etiology of oral cancer in the young patient: Is tongue cancer becoming the other cancer in women?" in which they noted that poor nutrition has been associated with cancer development, and an increase of fruits and vegetables in the diet has been shown to provide protection from the development of cancer. Iron deficiency associated with Plummer-Vinson syndrome, which typically affects middle-aged women, also has been associated with oral cancer. Immunosuppression has been linked to tongue cancer in younger patients, which suggests that a compromised immune system puts patients at risk. Intraoral factors, such as defective or malfunctioning dentures and poor oral hygiene, also can be contributing factors. Chronic irritation caused by poorly fitting dentures, broken dental restorations, and other frictional irritations is known to contribute to its development. These factors are generally regarded as modifiers rather than initiators. They are unlikely to cause cancer; however, if cancer is started from another cause, these factors probably hasten the progression of disease. Genetic predisposition is considered a contributing factor for most cancers, and oral cancer is not any different. Patients who have Fanconi's anemia, which is an autosomal recessive disorder characterized by constitutional aplastic anemia and congenital abnormalities, have an increased risk of developing squamous cell carcinomas,

especially intraorally. Oral cancers occur more frequently in the tongue in these patients. They also suggested differences in tolerances to risk factors, hormonal another systemic diseases and Rosenquist'snd immunologic changes, study, which evaluated risk factors, shows a tendency for women to have a greater risk than men for developing oral and oropharyngeal carcinoma at any given level of tobacco consumption. Hormonal and immunologic changes associated with pregnancy have been suggested as possible etiologic factors. It has been suggested that the physiologic changes that occur during pregnancy could lead to neoplastic growth in the oral cavity. Association of oral cancer to other systemic diseases in women has been mentioned. Diabetes mellitus has been associated in the development of periodontal disease and oral inflammatory and neoplastic lesions. The association between diabetes mellitus and premalignant oral lesions has been observed among women but not men. The underlying mechanisms for this association are not clear however, specific risk factors other than the traditional ones are poorly defined.

Hirota et al in 2008[17] published a paper titled "Risk factors for oral squamous cell carcinoma in young and older Brazilian patients: A comparative analysis" in which they conclude that although the young and older patients share a similar habit for the consumption of tobacco and /or alcohol, the pattern of consumption and time of exposure to these two risk factors suggested that these etiologic factors are less clearly implicated in the development of oral cancer in the young patients than in older ones. By and large, the cause of OSCC is complex and multi-factorial, and for young patients the cause of OSCC seems to present a different pattern from that found in older patients. Other risk factors which have been investigated by other authors in patients with OSCC were viral

agents (HPV, HSV) type of diet, work environment, immunosuppressive drugs, Fanconi's anemia, and genetic antecedents (familial). These investigations, however, did not indicate any consistent link between the risk factors studied and the development of OSCC in young patients. While one must remain aware of these foregoing considerations, the high rate (84.6%) of positive familial history for malignant neoplasm in these young patients (compared to 29.6% in older patients) does appear significant. Such a relationship would presumably be due to the fact that these risk factors carries great weight for young patients since the other risk factors (mainly habitual alcohol and tobacco use) require long periods of exposure.

Heymann et al in 2009[2] conducted a study titled "Carcinoma of the tongue" in which they found that patients with SCC of the head and neck who never smoked or drank are commonly young women with oral tongue cancer, elderly women with gingival/buccal cancer, or young to middle-aged men with oropharyngeal cancer. They surmise that while several potential exposures may be responsible for these findings, it is likely that no single factor is responsible for SCC of the head and neck in patients who have never smoked or imbibed alcohol.

Warnakulasuriya et al in 2009[1] "Global epidemiology of oral and oropharyngeal cancer" in which they noted that the risk of oral cancer due to both tobacco and alcohol is estimated to be more than 80%. Heavy drinkers and smokers have 38 times the risk of abstainers from both products. All forms of tobacco are carcinogenic and evidence for smokeless tobacco causing oral and pharyngeal cancer have recently been evaluated and confirmed. The consumption of fruit and vegetables is found to be associated with a reduced risk of oral cancer, and each portion of fruit or vegetable

reduces the risk by at least a quarter. This suggests a diet deficient in antioxidants is a further factor that predisposes towards the development of oral cancer and for precancer. Other factors such as HPV infection may also be involved, particularly for tonsil and oropharynx in young people. Six case-control studies have examined the relationship between tooth loss, periodontal disease and oral cancer, and some have reported significant associations. Among young people (under the age of 45 years) there is a small sub-group of patients (about 25%) who had little, if any, exposure to the major risk factors.

BIOLOGICAL BEHAVIOR

Byers et al in 1975[33] conducted a study titled "Squamous Cell Carcinoma of the Oral Tongue in Patients Less Than Thirty Years of Age". The analysis shows that the anaplastic squamous cell carcinoma of the oral tongue appears to have a higher incidence in persons less than thirty years of age and behaves biologically poorly in a virulent or aggressive manner.

McGregor et al in 1987[6] performed a study of 13 cases of the intra-oral squamous cell carcinoma in patients under 40 years of age. They concluded that young patients with oral cancer do not generally behave differently from similar stage matched lesion in older patients.

Kuriakose et al in 1992[27] did a comparison study of oral squamous cell carcinoma in younger and older patients in India and noted the significant difference in the morphological type of the tumor. 26 of 37 tumors in the <35 age group were

infiltrative whereas, in the >60 age group, only 6 patients had infiltrative lesions. The data indicates that tumors in younger patients behave more aggressively.

Bursynski et al in 1992[21] studied the squamous cell carcinoma of the upper aerodigestive tract in patients 40 years of age and younger and noted that anaplastic squamous cell carcinoma appears to have a higher incidence in the younger age group.

Iype et al in 2001[29] conducted a study of oral cancer among patients under the age of 35 years. The study suggested that oral cancers in young patients show a general trend of aggressive course and the proportion of advanced cases in the present series was considerably higher than reported earlier. At the time of presentation 66.3% cases were in advanced stages (III and IV).

Sasaki et al in 2005[30] did a multi-centric study of clinico-pathological features of squamous cell carcinoma of the oral cavity in patients < 40 years of age and concluded that there was a tendency for tumors in younger individuals to be well differentiated in contrast to lesions in the old group which were more often moderately differentiated.

Chitapanarux et al in 2006[23] conducted a retrospective research titled "Oral cavity cancers at a young age: Analysis of patient, tumor and treatment characteristics in Chiang Mai Hospital". The research was conducted from 1999 – 2003 with patients under the age 45 and the results showed that 15 of the 20 cases were well differentiated.

Regan et al in 2006[25] did a study titled "Squamous cell carcinoma of the head and neck in young Irish adults". The study proved that the biology of SCC of the head and neck in young people differs from that in older people and that there was a trend towards lower T stages at diagnosis in the younger group (p=0.008), and a higher

proportion of the younger patients had well-differentiated tumors (not significantly so) (p=0.009).

Papageorge et al in 2007[16] studied the etiology of oral cancer in the young patient titled "Is tongue cancer becoming the other cancer in women?" and came to the conclusion that though the clinical behavior of tongue cancer depends on many variables, including a patient's age, exposure to risk factors, and histological grade of the tumor, tongue cancers behave more aggressively in younger patients.

Ribeiro et al in 2008 after the study titled "Clinical and histopathological analysis of oral squamous cell carcinoma in young people: A descriptive study in Brazilians" suggest that oral SCC in young patients did not behave differently from oral SCC seen in the overall population.

Seyedmajidi et al in 2008[42] conducted a study on the squamous cell carcinoma of the tongue and came to the conclusion that patients belonging to younger age ranges are considered to have more aggressive diseases compared to patients in the older age ranges.

Ribeiro et al in 2009[26] after the study titled "Clinical and histopathological analysis of oral squamous cell carcinoma in young people: A descriptive study in Brazilians" found that in patients in the young age group, half of the oral SCCs were moderately differentiated and that 30% were poorly differentiated.

MITOSES

Siriwardena et al in 2006[24] did a study titled "Demographic, aetiological and survival differences of oral squamous cell carcinoma in the young and the old in Sri Lanka" in which they found that a significantly higher number of mitoses in the older

patients compared with the younger patients and a large majority of patients of the older group were betel chewers.

In contrast the present study did not show significant difference in mitoses when young patients compared with the older patients and majority of patients of the younger group were not having traditional risk factors.

METASTASIS

McGregor et al in 1983[6] did a retrospective study on squamous cell carcinoma of the tongue and lower oral cavity in patients under 40 years of age and found that metastases occurred in 38 percent of the patients and were present in six of seven tumor-related deaths.

Kuriakose et al in 1992[27] conducted a study titled "Comparison of Oral Squamous Cell Carcinoma in Younger and Older Patients in India" and came to the conclusion that despite there being an even distribution between the age groups concerning the staging of the tumors, in the younger age group the spread was more commonly to the local nodes particularly as the tumor size increased. The difference in the incidence of nodal involvement in T3 tumors between the two age groups was statistically significant ($P<0.005$). Higher incidence of lymph node metastasis and less favorable response to treatment in the <35 age group was a significant discovery.

Shiboski et al in 2005[12] did a multi-centric and retrospective study titled "Tongue and Tonsil Carcinoma – Increasing Trends in the U.S. Population Ages 20-44 years". The analysis shows that among younger adults, the proportion of tongue SCC diagnosed at a localized stage (48%) was similar to that of SCC that had metastasized (46%), whereas

greater than one-half of the tongue SCC among older adults had already metastasized at the time of diagnosis.

Iype et al in 2001[29] study titled "Oral cancer among patients under the age of 35 years" suggests that oral cancers in young patients show a general trend of aggressive course, poor prognosis and had regional lymph node involvement.

CYCLIN D1 EXPRESSION

Itou et al in 1999[43] did a study titled "Immunohistochemical study of cyclin D1 product in tongue squamous cell carcinoma". In their study they said, in the cancer specimens, positive cells were scattered, and the status of staining differed according to the site. Cyclin D1 was frequently positive in patients with advanced disease, such as T3 and T4 or stage 3 and 4. The positive cell percentage was associated with lymph node metastasis and the mode of invasion but not with the degree of differentiation.

Mineta et al in 2000[44] conducted study titled "Cyclin D1 over expression correlates with poor prognosis in patients with tongue squamous cell carcinoma". Their results showed that the tumor with higher CCND1 expression revealed more aggressive behavior. N classification correlated with CCN1 expression. CCND1 over expression is associated with poor survival associated with progression of lymph node spread in patients with tongue squamous cell carcinomas. It suggests that CCND1 shows the clinical indicator of the cancer spread. CCND1 expression may be a useful biologic marker for prognosis. It suggests that CCND1 shows the clinical indicator of the cancer spread.

Vicente et al in 2002[45] did a study titled **"**Expression of cyclin D1 in squamous cell carcinoma of the oral cavity: clinicopathological and prognostic significance". In their study they concluded over expression of cyclin D1 was significantly associated with regional lymph node metastases (P=0.00005) and advanced tumor stage (P=0.00007). The relative risk for nodal metastases in the cases that over expressed cyclin D1 was 2.6. They found Cyclin D1 expression and over expression in 71.4% (25/35) and 17.1% (6/35), respectively. Cyclin D1 over expression correlated with tumor size and lymph node spread. Therefore, they concluded that cyclin D1 is useful not only as prognostic factor, but also as a marker to help determine the appropriate treatment for patients with OSCC. However, this will require further clinical studies, specifically designed to test this hypothesis.

Goto et al in 2002[3] published a paper titled "Expression of cyclin D1 and GSK-3b and their predictive value of prognosis in squamous cell carcinomas of the tongue". In their study they concluded in lingual SCCs, cyclin D1 reaction varied in intensity among the tumors. Out of 41 SCCs,27 (65.9%) showed abundant of cyclin D1, in which various numbers of strongly-positive tumor cells were identified more frequently than in normal epithelia. Cyclin D1 - positive cells tended to be distributed in the periphery of tumor nests in SCCs of the well differentiated type and throughout tumor nests in moderately and poorly differentiated SCCs.

Wang et al in 2006[46] conducted a study titled "Activation of ERK1/2 and cyclin D1 expression in oral tongue squamous cell carcinomas: Relationship between clinicopathological appearances and cell proliferation". They said no significant differences in the level of cyclin D1 expression were found with respect to T stage,

lymph node metastasis and histological features, although lymph node metastasis was more prevalent in the high expression group. The expression of cyclin D1 was significantly stronger in OTSCCs than in normal tongue epithelium (Table 2, $P < 0.05$), these findings suggest that cylcin D1 plays an important role in cell proliferation in OTSCCs. The positive expression of cyclin D1 in OTSCCs showed a statistically significant association with tumor thickness (>5 mm $P < 0.05$) and lymph node metastasis ($P < 0.05$) but did not show a statically significant correlation with age, gender, tumor size, clinical stage or histological grade and metastasis.

Silva et al in 2007[47] did a study titled "Tissue Biomarkers for Diagnosis & Management of Oral Squamous Cell Carcinoma". In their study they concluded over expression of cyclin D1 has been associated with lymph node metastases.

Angadi et al in 2007[48] conducted a study titled "Cyclin D1 expression in oral squamous cell carcinoma and verrucous carcinoma: correlation with histological differentiation". In their study they observed a proportional increase in the percentage of positivity with increase in the cytological grade, which was in accordance with 2 other studies of OSCC by Lam et al and Miyamoto et al. Nine cases of poorly differentiated SCC were evaluated in our study, out of which 2 cases (22.2%) showed moderate staining, but the predominant staining intensity was intense, which was observed in 6 cases (66.6%). Only 1 case (11.1%) showed negative immunoreactivity. Their study thus showed a uniformly increasing intensity in relation to the cytological grade, that is, an increase in the intensity with poor cytological grade.

p27 EXPRESSION

Kudo et al in 2003[49] did a study titled "Establishment of an oral squamous cell carcinoma cell line with high invasive and p27 degradation activities from a lymph node metastasis" in which they demonstrated that reduced expression of $p27^{kip1}$ occurred in 87% of oral squamous cell carcinomas (OSCCs) and correlated with their malignant behaviors. This finding indicated that reduced expression of $p27^{kip1}$ may play an important role in an abnormal proliferation through a loss of cell cycle regulation. They hypothesized that down-regulation of $p27^{kip1}$ may concern the cancer invasion directly or indirectly as well as abnormal proliferation. They have previously reported that the loss of $p27^{kip1}$ protein is also closely associated with metastasis in OSCCs. These findings suggest that reduced expression level of $p27^{kip1}$ may correlate with ability of cancer invasion. High ability of cancer invasion may lead to invasion into blood capillary or lymphatic vessels in the process of metastasis.

Their findings may also suggest that reduced expression of $p27^{kip1}$ is a useful marker for the evaluation of invasive ability of oral cancer.

MATERIALS AND METHODS

The medical records of 219 consecutive patients diagnosed with squamous cell carcinoma (SCC) of the tongue between October 1970 and December 2009 was retrieved from the institutional oral pathology registry. Clinical (age at presentation, gender, site, and symptoms and their duration, habits and history of trauma) and pathologic characteristics (histological grade) of all the 219 samples were abstracted from the registry and reviewed microscopically. They were divided into two groups; patients over 35 years of age and less than 35 years of age. Off the 219 tongue cancers, 26 were found in patients less than 35 years of age. The two groups were compared clinicopathologically and a subset of ten cases was selected on the basis of TNM status for immunohistochemistry (Markers- p27, Cyclin D1) to observe variance at the molecular level.

The hematoxylin and eosin stained slides of the respective cases were reviewed, and where necessary additional H&E sections were made by retrieving the available wax blocks from the department archives.

Using the Leica microtome, 4 micron meter thick sections were cut from the blocks for Ehrlich Hematoxylin and Eosin staining.

Procedure for Hmatoxylin and Eosin staining

- Sections are deparaffinised with xylene.
- Hydration wit descending grades of alcohol.

- The sections were drained and transferred to hematoxylin, where they are left for 10 minutes.
- The slides were then drained and washed in running water until the sections are blue.
- The sections are dipped in acid alcohol where they are agitated for a few seconds and again washed in running water until blue again.
- The sections are counterstained with eosin for 30 seconds.
- The sections are washed in running water for 3-4 minutes, to differentiate the eosin.
- After draining, the sections are dehydrated in ascending grades of alcohol.
- The sections are cleared with Xylol, where they are given two changes for 30 seconds each.
- The sections being clear, the slides are dried and mounted wit Distrene 80 Dibutyl Phthalate Xylol (DPX) under a cover slip.

The stained and mounted slides for all cases were examined under the light microscope to confirm the previous histopathologic diagnosis.

Results

1. Nuclei: Blue
2. Cytoplasm: Varying shades of pink
3. Collagen: Pink

The previously rendered diagnosis were re-evaluated and confirmed or modified.

IMMUNOHISTOCHEMICAL ANALYSIS

The tumor tissue blocks (22 cases were selected randomly from each group) were cut into 4µM thick sections. For immunohistochemical examination of Cyclin D1 and

p27, the En Vision + system (Biogenex-USA) was used. The tissue sections were deparaffinized and rehydrated in a graded series of alcohols. Endogenous peroxidase activity was blocked with 0.3% H_2O_2 in methanol for 30 min. The sections were micro-waved three times for 5 min each in citrate phosphate buffer (pH 6.0) for antigen retrieval. The sections were then incubated with protein block serum-free medium for 10 min to block non-specific binding. Monoclonal antibodies of Cyclin D1 (Biogenex-USA-Polyclonal) and p27 (Biogenex-USA- DCS 72) were applied as primary antibodies and incubated at 4º C overnight. After washing with PBS, peroxidase-conjugated secondary antibody was applied to the sections, which were then incubated for 1 hr at room temperature. Peroxidase was visualized with diaminobenzidine (DAB). Sections were counterstained with Mayer's haematoxylin, dehydrated and mounted. Expression of Cyclin D1 was assessed as Positive and negative cells were counted under a microscope (x100), and the percentage of positive cells was calculated. Patients showing a positive cell percentage of 5% or more were considered to be positive for cyclin D1. (Itou et al 1999)

The degree of immunohistochemical staining was evaluated a positive percentage of the nuclei. Each tumor specimen was classified into two groups on the degree of immunohistochemical staining for CCND1 as follows: low intensity (0-50% of tumor cell nuclei positive), and high intensity (50-100%). Tumors which showed high intensity staining of CCND1 expression were considered to over express CCND1.[44, 45]

The nuclear staining of $p27^{kip1}$ was scored on a semi-quantitative scale by evaluating the percentage of stained nuclei within representative areas of each tumor. The expression of $p27^{kip1}$ was graded as ++ (over 30% of tumor cells showed strong or diffuse

immunopositivity), + (5-30% of tumor cells showed moderate or patchy immunopositivity) and – (less than 5% of the tumor cells showed weak or focal immunopositivity or no staining).[49]

STATISTICAL ANALYSIS

The correlation between the young and the old groups was tested by the chi-squared test. A P-value of <0.05 was considered as significant.

OBSERVATIONS AND RESULTS

Squamous cell carcinoma comprised a total of 2225 cases out of 12904 cases recorded in the institution over the period of 39 years.

INCIDENCE OF ORAL CANCER

The incidence of SCC was assessed in four decades (1970-2009). Our study showed increase in the frequency of SCC over the decades. Frequency of young cases increased from 24 (1970-79) to 65 cases (2000-09). But the percentage of young cancer cases decade wise is decreased from 18.18% (1970-79) to 5.76% (2000-09). Frequency of old cases increased from 108 (1970-79) to 1063 cases (2000-09). Percentage of old cancer cases decade wise is increased from 81.81% ((1970-79) to 94.23% (2000-09). Both the groups showed a gradual increase in the number of cases recorded decade wise.

Table 1: Oral Cancer Cases – Decade wise.

Figure 1: Total Cancer Cases – Decade wise.

Table 2: Percentage of Oral Cancer Cases – Decade wise.

Figure 2: Comparison of Percentage of Young & Old Cancer Cases – Decade wise.

Figure 3: Total Young Cancer Cases.

INCIDENCE OF TONGUE CANCER

The incidence of SCC of the tongue was assessed in four decades (1970-2009). SCC of the tongue comprised 9.84% of the total 2225 SCC. Off the 219 tongue SCC, 11.88% occurred in younger age group and 88.12% occurred in older age group. Our

study showed increase in frequency of SCC of the tongue over the decades. Total tongue cancer cases increased from 7 (1970-79) to 136 (2000-09). In the current study, gradual increase in the number of young cases recorded being 1 in the first decade with a 0.73 % compared to a higher number of cases being 19 during the current decade with 1.67 %. Frequency of old cases increased from 6 (1970-79) with 4.41% to 116 (2000-09) with 10.23%.

Figure 4: Tongue Cancer Cases Decade wise Total Cancer Cases – Young Patient.

Table 3: Tongue Cancer Cases – Decade wise

Figure 5: Shows Total Tongue Cancers – Decade wise.

Figure 6: Number of Young Tongue Cancer Cases – Decade wise

Table 4: Total Tongue Cancer Cases – Decade wise

Table 5: Percentage Tongue Cancer Cases – Decade wise

Figure 7: Percentage of Tongue Cancer Cases – Below 35 Years

Figure 8: Comparison of Number of Young & Old Tongue Cancer Cases – Decade wise

GENDER DISTRIBUTION OF TONGUE CANCER FOR YOUNG PATIENTS

In the present research it was observed that there were 18 male patients and 8 female patients of 26 patient populations. In young patients males were affected with 69.23% while females are affected with 30.70%. In old patients male were affected with 61.64% while female were affected with 25.57%. The current study showed more of male predilection for both young and old patients.

Table 6 a: Gender Distribution - Young Patients with Tongue Cancer.

Table 6 b: Gender Distribution - Old Patients with Tongue Cancer.

SITE DISTRIBUTION FOR TONGUE CANCER IN YOUNG PATIENTS

The present study showed that 21 of 26 young patients were affected in the lateral border of the tongue, 1 patient in the right side of the tongue, 1 patient in the ventral surface of the tongue while the exact location in 3 patients was undeterminable due to non-availability of information. Lateral border of tongue affected with 80.77%, Side of the tongue affected with 3.84%, and ventral surface of the tongue affected with 3.84%. In old patients lateral border of tongue affected with 55.71%, Side of the tongue affected with 7.30%, and ventral surface of the tongue was affected with 13.24%.

Tongue cancer cases in both the young and old group have more predilections towards lateral border of tongue.

Table 7 a: Sites Affected in Tongue Cancer Cases – Young Patients.

Table 7 b: Sites Affected in Tongue Cancer Cases – Old Patients.

Table 8 a: Percentage of Site Predilections – Young Patients.

Table 8 b: Percentage of Site Predilections – Old Patients.

RISK FACTOR ASSESSMENT

The present study shows that 17 of 26 cases have no evidence of association between any of the traditional risk factors and the development of SCC of the tongue in young patients. The young cases were not having habits with 88.46%. And history of sharp teeth is noted to be the causative factor among 4 female and 2 male patients. While 1 male patient was noted to have both sharp teeth and associated with traditional risk factor of alcoholic abuse, 2 male patients having been chewing pan but only for insignificant durations. Young patients were having habit etiology with 11.54%. Young

cases were not associated with traditional risk factors with 88.46%. Young cases were having etiology of irritating dental factors with 26.92%. Old cases were associated with traditional risk factor with 22.79%, cases without habits 1.03%, habits not mentioned for 76.16%, cases with irritating dental factor etiology with 7.77%.

In the present study for young patients irritating dental factors were considered to be the major risk factor while for the old patients traditional risk factors were considered to be the major risk factors.

Table 9: Young Tongue Cancer Cases – Etiology & Duration.

Table 10 a: Percentage Evaluation of Etiological Factors – Young Patients.

Table 10 b: Percentage Evaluation of Etiological Factors – Old Patients.

HISTOLOGICAL GRADE ASSESSMENT

22 cases were selected for histological grade assessment of which 11 cases are of young group and 11 of old group. In the present study well differentiated old cases with 61.42%, well differentiated young cases with 62.5%, moderately differentiated old cases with 31.90%, moderately differentiated young cases with 33.33%, poorly differentiated old cases with 6.67%, and poorly differentiated young cases with 4.17%.

In the present study the younger patients as compared with the older patients did not show much difference in the histological grades. Well, moderately differentiated carcinomas are more or less equally distributed within the two age groups.

Poorly differentiated cancer has slightly more predilection for older age group.

Table 11: Selected Cases of Tongue Cancer - Histopathological & Immunohistochemical Assessment.

Table 12: Histological Grade Assessment for Total Tongue Cancer.

MITOSES ASSESSMENT IN YOUNG AND OLD CASES

22 cases were selected for mitoses assessment of which 11 cases are of young group and 11 of old group. Present study showed no significant difference in mitoses in younger patients who were not associated with any or prolonged traditional risk factors compared with the older patients who were associated with traditional risk factor. The number of cases showed 26-30 mitoses/HPF in young patients 2 and in old patients 1.

Table 13: Selected Cases of Tongue Cancer – Mitoses Assessment.

Table 14: Comparison of Mitoses Assessment – Young & Old Patients

TNM STATUS ASSESSMENT

22 cases were selected for TNM status assessment of which 11 cases are of young group and 11 of old group. T stage is not specified for 16 cases out of 26 cases for young patients, so it is not possible to arrive at definite conclusion.

Nodal metastasis is not specified for 16 cases out of 26 cases for young patients, so it is difficult to arrive for any conclusion.

Table 15: Selected Cases of Tongue Cancer – TNM Status Assessment

CYCLIN D1 EXPRESSION EVALUATION

22 cases were selected for cyclin D1 expression assessment of which 11 cases are of young group and 11 of old group. The present study did not show a statistically significant correlation with age, gender, tumor size, or histological grade.

Young cases and old cases both showed same percentage (28.57%) cases for high Cyclin D1 expression. A significant difference was not found with regard to the mitoses, and Cyclin D1 expression when young patients compared with older patients.

Table 16: Selected Cases of Tongue Cancer – Cyclin D1 & p27 Evaluation

Table 17 a: Selected Cases of Tongue Cancer – Cyclin D1 Evaluation of Young Patients.

Table 17 b: Selected Cases of Tongue Cancer – Cyclin D1 Evaluation of Old Patients.

$p27^{kip1}$ EXPRESSION EVALUATION

22 cases were selected for $p27^{kip1}$ expression assessment of which 11 cases are of young group and 11 of old group. In the present study old cases with p27 expression ++ are 2 cases with 18.18%. Young cases with p27 expression ++ are 3 cases with 27.27%. Expression of $p27^{kip1}$ evaluation did not show significant difference in its expression in young patients when compared with old patients.

The present study did not show a statistically significant correlation with age, gender, tumor size, or histological grade in Cyclin D1, p27kip 1 expression.

Table 16: Selected Cases of Tongue Cancer – Cyclin D1 & p27 Evaluation.

Table 18 a: Selected Cases of Tongue Cancer – p27 Expression in Young Patients.

Table 18 b: Selected Cases of Tongue Cancer – p27 Expression in Old Patients.

DISCUSSION

Oral/pharyngeal in young people is about 6% of oral cancers occur in young people under the age of 45 years. In high-incidence countries of the world, many cases are reported before the age of 40. The rising incidence in oral and oropharyngeal cancer and mortality rates in young adults is reported from many countries in the European Union and parts of United States. In Scotland, where this trend was first reported, the incidence rate between 1990 and 1999 in males under 45 has more than doubled from 0.6 to 1.3 per ratio is lower in men than in women, suggesting that some male characteristics may predispose preferentially to pharyngeal cancer.[1]

The present study is based on cases among the population registered in the Department of Oral & Maxillofacial Pathology of the Tamil Nadu Government Dental College & Hospital - Chennai, South India. This study on a sample size of 219 cases spread over a period of 4 decades.

Squamous cell carcinoma comprised a total of 2225 cases out of 12904 cases recorded in the institution over the period of 39 years. Of 2225 cases of SCC, tongue carcinoma cases were 219. SCC of the tongue comprised 9.84% of the total SCC. Off the 219 tongue SCC, 11.88% occurred in younger age group and 88.12% occurred in older age group. That is 26 were found in patients less than 35 years of age remaining cases were found in older age group. It also revealed a gradual increase in the number of cases recorded being 1 in the first decade with a 0.73 % compared to a higher number of cases being 19 during the current decade with 1.67 %. The reasons that oral cavity SCCs develop in these patients remain unclear. The present study also showed that squamous

cell carcinoma of the tongue occurs at 1.69 % in young patients of the total biopsied specimens registered in the department.

According to most authors they considered age of young patients with SCC in general is less than 40 years of age, even though others use as reference ages under 20 or 30 years. Age average in cases registered in literature as young bearers of SCC ranges from 30 to 34.2.[4, 5]

Hence, the age of young patients with SCC, considered in this present study is 35 years & below.

The review of literature showed the increase in the incidence of oral tongue SCC in young patients during recent decades. The increase in numbers of cases will, in the future, be proportionately greater.[6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 1]

Accordingly, in this present study an increase of incidence of oral tongue SCC in young patients was noticed. In current study gradual increase in the number of cases recorded being 1 in the first decade with a 0.73 % compared to a higher number of cases being 19 during the current decade with 1.67 %.

In review of literature some authors describe that carcinoma of the tongue was often found in the early years of life, and occurred as frequently in females as in males.[19,6,21,22,23,15]

While other authors describe that the incidences of carcinoma of the tongue frequent male gender more often than female gender.[18, 20, 24, 25, 26]

In accordance with this study in the present study it was observed that there were 18 male patients and 8 female patients of 26 patient populations. In young patients males were affected with 69.23% while females were affected with 30.70%. In old patients

males were affected with 61.64% while females were affected with 25.57%. The current study showed more of male predilection for both young and old patients for tongue cancer.

The review of literature showed that all patients with SCC of the oropharynx had a previous history of tobacco and alcohol use, whereas tumors arising in patients without these carcinogenic factors were more often located on the tongue and the floor of the mouth. This observation agreed with previous research that showed an increase in the site of the tumor depending on the etiologic factor analyzed.[7]

While some authors say that carcinomas of the anterior two-thirds of the tongue were significantly more common in younger patients.[25]

Others says that approximately 45% of tongue cancers occur in the posterior lateral border of the tongue, and 25% occur in the posterior one third or base of the tongue.[16]

In accordance with this the present study showed that 21 of 26 young patients were affected in the lateral border of the tongue, 1 patient in the side of the tongue, 1 patient in the ventral surface of the tongue while the exact location in 3 patients was undeterminable due to non-availability of information. Lateral border of tongue affected with 80.77%, side of the tongue affected with 3.84%, and ventral surface of the tongue affected with 3.84%.

In old patients lateral border of tongue affected with 55.71%, Side of the tongue affected with 7.30%, and ventral surface of the tongue was affected with 13.24%.

Tongue cancer cases in both the young and old group have more predilections towards lateral border of tongue.

The review of literature shows that usual concomitant factors, such as heavy smoking, drinking, tobacco chewing, and poor dental hygiene, were absent for younger patients.[33, 27, 21, 7, 39, 8, 29, 40, 9, 12, 4, 31, 23, 24, 25, 1]

Whereas, some authors suggest that long-standing irritation from chronic periodontal disease, poor oral hygiene, ill-fitting dentures, gold crowns, orthodontic appliances, irritating and broken dental restoration, sharp teeth, carious teeth, dietary factors, viral factors, genetic predisposition, immunodeficiency, Iron deficiency, occupational exposure, and socioeconomic condition have all been implicated as cofactors in the genesis of tongue cancer. They concluded that multi-factorial aetiology in young patients must be considered.[19, 20, 34, 36, 37, 38, 4, 24, 16, 17, 2, 1]

In accordance with previous studies this present study showed that 17 of 26 cases have no evidence of association of the traditional risk factors in young patients. The young cases were not having habits with 88.46%. And history of sharp teeth is noted to be the causative factor among 4 female and 2 male patients. While 1 male patient was noted to have both sharp teeth and associated with traditional risk factor of alcoholic abuse, 2 male patients having been chewing pan but only for insignificant durations. Young patients were having habit etiology with 11.54%. Young cases were not associated with traditional risk factors with 88.46%. Young cases were having etiology of irritating dental factors with 26.92%. In the present study for young patients irritating dental factors were considered to be the major risk factor.

Old cases were associated with traditional risk factor with 22.79%, cases without habits 1.03%, habits not mentioned for 76.16%, cases with irritating dental factor

etiology with 7.77%. While for the old patients traditional risk factors were considered to be the major risk factors.

The review of literature shows that there was a tendency for tumors in younger individuals to be well differentiated in contrast to lesions in the old group which were more often moderately differentiated.[30, 23, 25]

In contrast Ribeiro et al in 2009[26] have concluded that in patients in the young age group, half of the oral SCCs were moderately differentiated and that 30% were poorly differentiated. Siriwardena et al in 2006[24] have concluded that well, moderately and poorly differentiated carcinomas are more or less equally distributed within the two age groups.

In the present study well differentiated old cases with 61.42%, well differentiated young cases with 62.5%, moderately differentiated old cases with 31.90%, moderately differentiated young cases with 33.33%, poorly differentiated old cases with 6.67%, and poorly differentiated young cases with 4.17%.

However, in the present study the younger patients as compared with the older patients did not show much difference in the histological grades. Well, moderately differentiated carcinomas are more or less equally distributed within the two age groups. Poorly differentiated cancer has slightly more predilection for older age group.

The review of literature showed significantly higher number of mitoses in the older patients compared with the younger patients and a large majority of patients of the older group were betel chewers.[24]

In contrast to this the present study showed no significant difference in mitoses in younger patients who were not associated with any or prolonged traditional risk factors.

The case of young people differs from that in older people and that there was a trend towards lower T stages at diagnosis in the younger group (p=0.008).[25]

T stage not specified for 16 cases out of 26 cases for young patients, so it is not possible to arrive at definite conclusion.

The review of literature shows that despite there being an even distribution between the age groups concerning the staging of the tumors, in the younger age group the spread was more commonly to the local nodes particularly as the tumor size increased. The difference in the incidence of nodal involvement in T3 tumors between the two age groups was statistically significant (P<0.005).[27, 29]

In contrast to the above mentioned literature the analysis of a certain author shows that among younger adults, the proportion of tongue SCC diagnosed at a localized stage (48%) was similar to that of SCC that had metastasized (46%), whereas greater than one-half of the tongue SCC among older adults had already metastasized at the time of diagnosis.[12]

Nodal metastasis is not specified for 16 cases out of 26 cases for young patients, so it is difficult to arrive for any conclusion.

Even though the present study showed higher proportion of tongue SCC at the localized stage in young patients whereas, older patients showed more of nodal involvement while comparing with only TNM status mentioned cases among both groups.

Oral carcinogenesis is a multistep process in which 6-10 genetic events lead to the disruption of the normal regulatory pathways that control basic cellular functions including cell division, differentiation, and cell death. In recent years, several alterations

in the expression of tumor suppressor genes and oncogenes in the development of OSCC have been described.

Aberration of normal cell cycle control reflects some of the genetic changes specific to cancer. Cyclin D1 (CCND1) accelerates the G1 phase by binding to CDK4 or 6. The CCND1//CDK4 OR 6 completed is activated by CDK activating kinase, which phosphorylates a threonine (aminoacid 172) in CDK. This activated complex phosphorylates the retinoblastoma (Rb) protein, causing the release of bound transcription factors of E2F1-3 from the Rb protein. The released E2F transcription factor, mainly E2F1, activates the gene products required for entry into the S phase. The CDK complexes phosphorylate other substrates such as p107 and p130, in addition to Rb protein; however their influence may not be so much as E2F. Over expression of CCND1 had been found in 16-64% of HNSCC cases. If CCND1 is overproduced or works unsuitably, cell division and proliferation would occur, in addition to other cellular and environmental factors, followed by other steps in the development of cancer.[44]

Cyclin D1, which is isolated from the parathyroid gland and located at chromosome 11q13, is considered to be an important modulating factor for cell proliferation.

Positive and negative cells were counted under a microscope (x100), and the percentage of positive cells was calculated. Patients showing a positive cell percentage of 5% or more were considered to be positive for cyclin D1.[43]

Each tumor specimen was classified into two groups on the degree of immunohistochemical staining for CCND1 as follows: low intensity (0-50% of tumor cell

nuclei positive), and high intensity (50-100%). Tumors which showed high intensity staining of CCND1 expression were considered to over express CCND1.[44, 45]

In the cancer specimens, positive cells were scattered, and the status of staining differed according to the site. Cyclin D1 was frequently positive in patients with advanced disease, such as T3 and T4 or stage 3 and 4. The positive cell percentage was associated with lymph node metastasis and the mode of invasion but not with the degree of differentiation.[43,44,47] Over expression of cyclin D1 was significantly associated with regional lymph node metastases (P=0.00005), and with poor cytological grade.[48, 45]

The positive expression of cyclin D1 in OTSCCs showed a statistically significant association with tumor thickness (>5 mm $P < 0.05$) and lymph node metastasis ($P < 0.05$) but did not show a statically significant correlation with age, gender, tumor size, or histological grade.[46]

In accordance with this the present study did not show a statistically significant correlation with age, gender, tumor size, or histological grade. Young cases and old cases both showed same percentage (28.57%) cases for high Cyclin D1 expression.

Inhibitors family cip/kip includes p27 kip1. This has 44% homology with p21 cip1, particularly in the N-terminal region, and is highly conserved between species. This 27-kDa protein act on cyclin E/cdk2, cyclin D/cdk4 and cyclin A/cdk2 complexes, causing G1 arrest by inhibiting phosphorylation pRb.[50]

The nuclear staining of $p27^{kip1}$ was scored on a semi-quantitative scale by evaluating the percentage of stained nuclei within representative areas of each tumor. The expression of $p27^{kip1}$ was graded as ++ (over 30% of tumor cells showed strong or diffuse immunopositivity), + (5-30% of tumor cells showed moderate or patchy

immunopositivity) and – (less than 5% of the tumor cells showed weak or focal immunopositivity or no staining).[49]

From the retrospective review of published paper it is understood that reduced expression of $p27^{kip1}$ occurred in 87% of oral squamous cell carcinomas (OSCCs) and correlated with their malignant behaviors. This finding indicated that reduced expression of $p27^{kip1}$ may play an important role in an abnormal proliferation through a loss of cell cycle regulation. They hypothesized that down-regulation of $p27^{kip1}$ may concern the cancer invasion directly or indirectly as well as abnormal proliferation. It is previously reported that the loss of $p27^{kip1}$ protein is also closely associated with metastasis in OSCCs. These findings suggest that reduced expression level of $p27^{kip1}$ may correlate with ability of cancer invasion.[49]

In the present study old cases with p27 expression ++ are 2 cases with 18.18%. Young cases with p27 expression ++ are 3cases with 27.27%.

The present study did not show a statistically significant correlation with age, gender, tumor size, or histological grade in Cyclin D1, p27kip 1 expression. The young cases showed no significant difference in its biological behavior when compared with old patients.

SUMMARY AND CONCLUSION

The present study was designed to determine differences between the two groups that could be attributed towards early development of cancers in patients less than 35 years of age. This study was based on a sample size of 219 tongue carcinoma cases out of 2225 SCC cases spread over a period of 4 decades registered in TNGDC&H, India.

26 cases were found in patients less than 35 years of age. The present study shows that while 11.88% occurred in younger age group, 88.12% occurred in older age group. It also revealed a gradual increase in the number of cases being 1 in the first decade with a 0.73% compared to a higher number of cases being 19 in the current decade with 1.67%.

Habit etiologies in young patients were 11.54% and old patients were 22.79%. Young cases not associated with habits were 88.46% while old cases were 1.03%. Habits not mentioned for old cases are 76.16%. Young cases having etiology of irritating dental factors were 26.92% while old cases were 7.77%. Irritating dental factors was also considered as major risk factor for younger group while traditional risk factors were considered for older group. In young group, lateral border of tongue affected with 80.77% and for old patients 55.71. Males in young group were affected with 69.23% while in old group were 61.64%. In both the young and old group the gender Male and in site lateral border of the tongue showed more predilection.

In the present study the histological grade of young group and old group did not show much difference.

Both young and old cases showed same percentage (28.57%) cases for high Cyclin D1 expression p27 expression ++. In old and young group respectively are 2 cases

with 18.18% and 3 cases with 27.27%. No significant correlation with age, gender, tumor size and histological grade with Cyclin D1 and $p27^{kip1}$ expression.

In conclusion, SCC of the tongue comprised 9.84% of the total 2225 SCC. Off the 219 tongue SCC, 11.88% occurred in younger group and 88.12% occurred in older group. Clinically, the lateral border of the tongue was the most frequent site involved while Gender involvement showed equal distribution. Etiologically, irritating dental factors was a major risk factor in younger age group and habits were major risk factors for the older age group. Both the groups show a gradual increase in the number of cases recorded decade wise.

Further, it is evident that the histopathological grading systems show that the two groups are equally distributed. The present study did not show a statistically significant correlation with age, gender, tumor size, or histological grade in Cyclin D1 and $p27^{kip\ 1}$ expression.

The documentation of these unusual cases may point to or confirm the role of less obvious pathogenetic factors. Much of the literature concerning dental factors in the aetiology of oral cancer is either anecdotal or lacking in controls. The retrospective analyses are difficult to evaluate because the genesis of oral cancer may follow a process of many years of irritation from multiple sources. Only a large prospective study would provide adequate data to resolve some of the issues related etiology and molecular differences.

High index of clinical suspicion in high incidence areas in younger aged group should lead to further investigation in order to identify the disease in early stage, which is perhaps the only way to ensure good prognosis.

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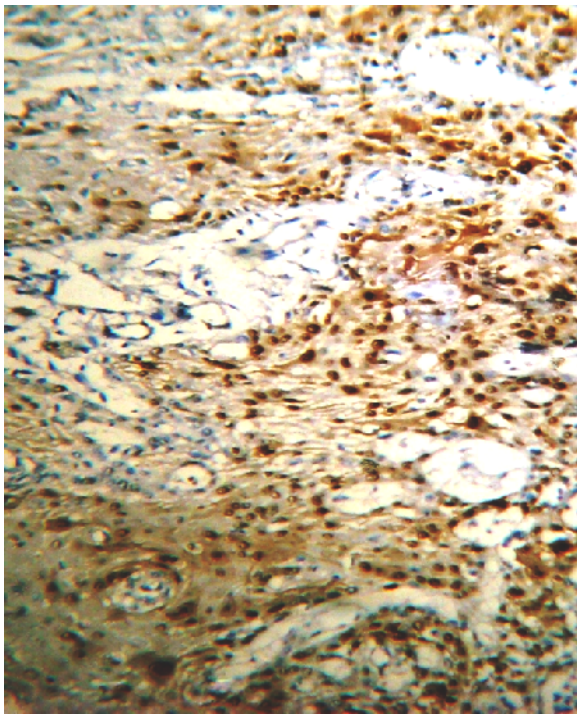
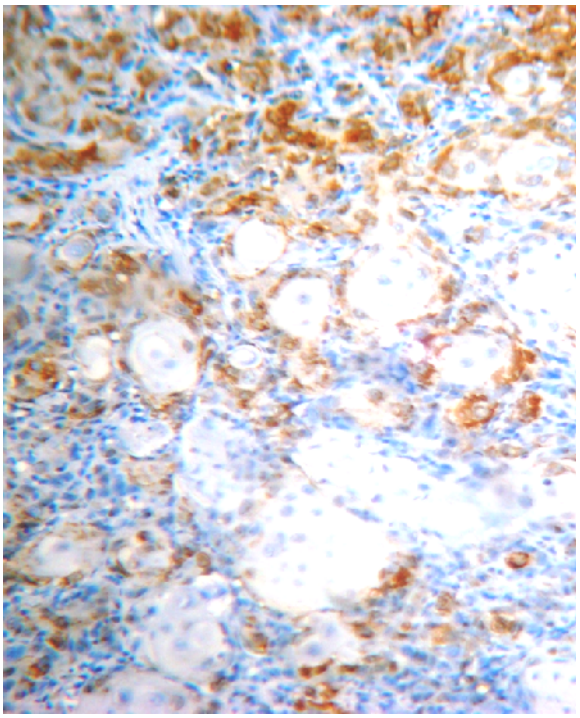
Primary and Secondary Antibodies used in Immunohistochemistry.



Cyclin D1 – High Intensity



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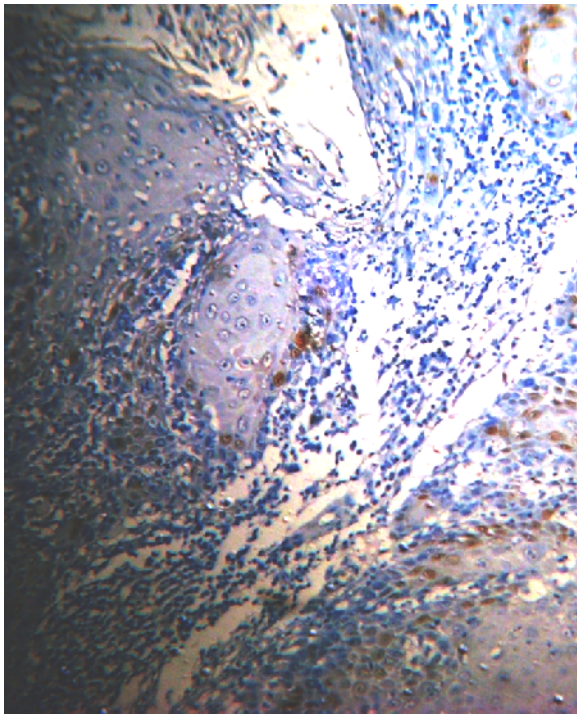

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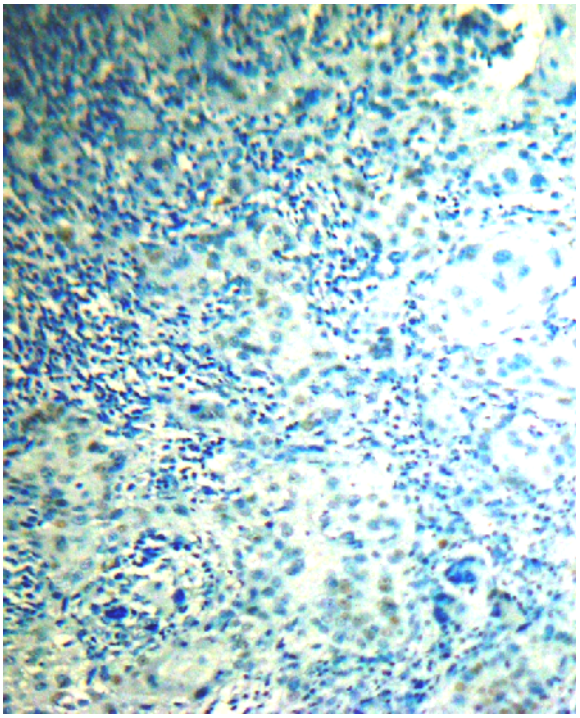

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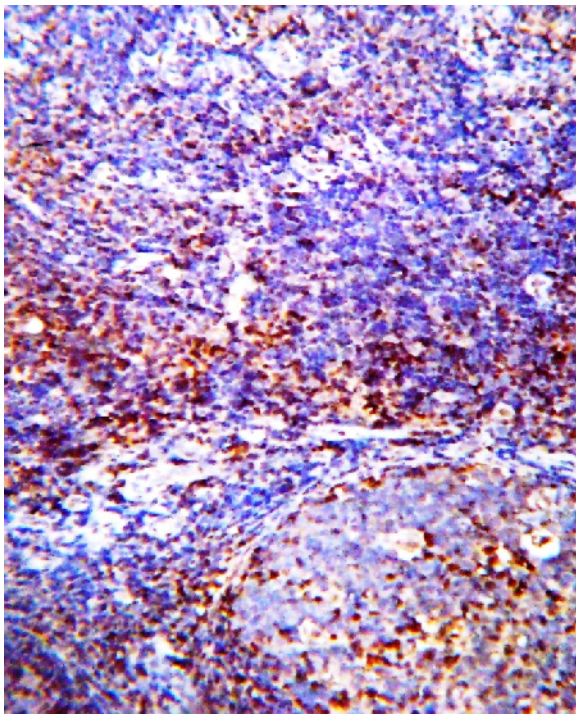
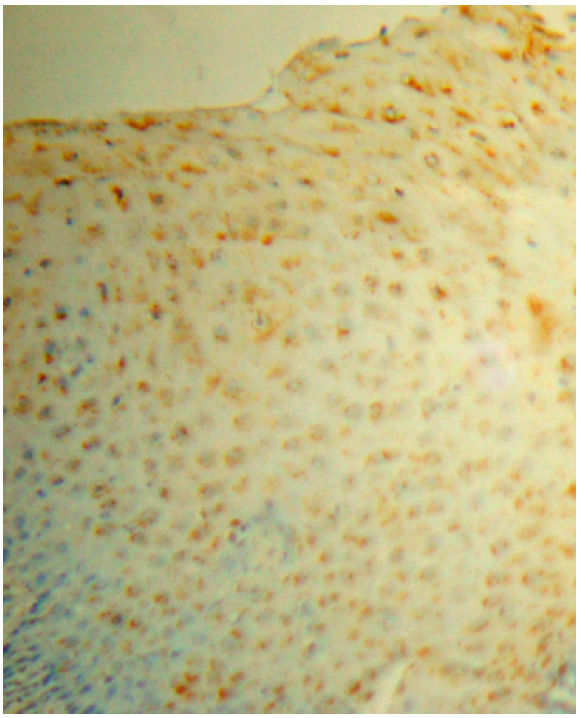
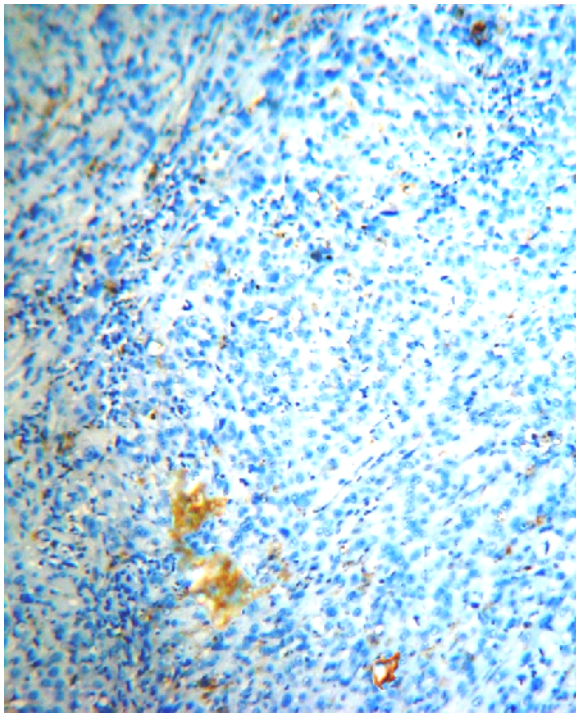


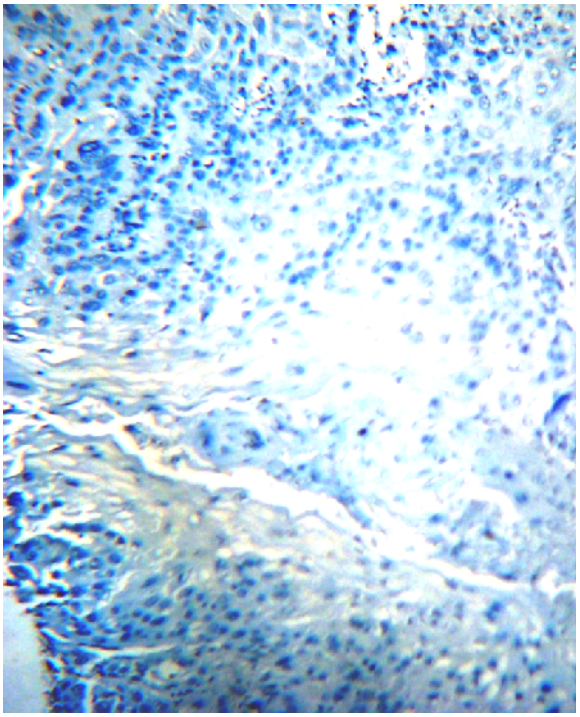
p27 – Control



p27 – Double Positive



p27 – Single Positive



p27 – Negative